Contribution of multiple inert gas elimination technique to pulmonary medicine · 4

Series editor: R Rodriguez-Roisin

Gas exchange abnormalities in pulmonary vascular and cardiac disease

Gérard Manier, Yves Castaing

Pulmonary vascular disease is generally defined as an anatomical narrowing of the pulmonary vasculature, especially the muscular arteries, either from lung disease or as a primary disease of the pulmonary vessels. In a broader sense it can also be defined as a change in the overall regional pulmonary vascular impedance, stemming from anomalies in the lumen or the walls of pulmonary vessels. We will therefore review different clinical situations causing pulmonary vascular disease where gas exchange can be evaluated using the multiple inert gas elimination technique (MIGET). Pulmonary embolism (PE), unilateral pulmonary artery occlusion, and polycythaemia are first discussed, with special reference to the effect of haemodilution. We then summarise the response to structural abnormalities in the pulmonary arteries in patients with primary pulmonary hypertension or cirrhosis of the liver. Cardiac failure occurring in these conditions tends to accentuate the disturbances in gas exchange as a result of the interplay between intrapulmonary and extrapulmonary factors which determine PaO_2 values. However, most primary cardiac diseases occur in patients with previously normal lungs. We therefore conclude with a separate discussion of the adaptation of pulmonary gas exchange processes to a change in cardiac output in the absence of any associated pulmonary abnormality.

Diseases with intravascular abnormalities

PULMONARY EMBOLISM

Consequences of heart-lung interactions

When clots lodge in one or more pulmonary arteries, the pathophysiological consequences will clearly depend on the duration and extent of the acute interruption of blood flow in the pulmonary vascular bed. The haemodynamic consequences are afforded by two principal factors: (1) the increase in pulmonary vascular resistance, and (2) the previous cardiovascular status of the patient. In patients without cardiovascular disease the thin walled right ventricle may fail under high workload and cardiac output (CO) may drop. In many other clinical

situations, however, CO remains in the normal range or even rises.¹ In the lung, apart from the continuation of the ventilation of non-perfused areas, embolism may lead to: (1) some degree of bronchoconstriction and atelectasis, with a concomitant redistribution of alveolar ventilation, and (2) enhanced pulmonary vasoreactivity, possibly due to hypoxaemia, release of humoral mediators by clot, or a distension reflex in the obstructed vessels. Moreover, in spontaneously breathing patients ventilatory drive increases. In many cases hypoxaemia is the only obvious manifestation of the complex interaction between the effects of embolism and the adaptive responses of the heart and lungs. The relative involvement of factors such as intrapulmonary shunt, ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequalities, and diffusion limitation to oxygen in individual cases has only recently begun to be clarified. This is largely due to the use of the MIGET in patients with angiographically demonstrated pulmonary embolism. Although only a few studies²⁻⁵ have been carried out with the inert gas method, there is a parallel between the pattern of gas exchange abnormalities and the course of the disease.

Early phase:

(1) *Ventilation-perfusion relationships in the non-embolised areas.* In the acute phase of the disease – that is, the first 48 hours following the embolic episode – the acute shrinkage of the pulmonary vascular bed induces functional disorders in the alveoli of occluded areas as well as in the remaining ventilated and perfused lung. Pulmonary gas exchange ultimately depends on the combined effects of two main mechanisms: (1) mechanical redistribution of pulmonary blood flow away from obstructed vascular areas towards non-occluded vessels; and (2) redistribution of alveolar ventilation induced by bronchoconstriction or atelectasis in occluded areas. However, inert gas studies of spontaneously breathing patients have shown that there is no typical pattern of distribution of either ventilation or perfusion after acute pulmonary embolism (PE). In our most recent study⁵ we found that the pattern depends

Laboratoire
d'Exploration
Fonctionnelle
Respiratoire, Service
de Réanimation
Médicale A, Hôpital
Pellegrin, Tripode,
33076 Bordeaux
Cédex, France
G Manier
Y Castaing

Reprint requests to:
Dr Y Castaing.

Figure 1 Ventilation-perfusion distribution in a patient with pulmonary embolism. The percentage of vascular obstruction was 30% and inert gas dead space was 56%. There was a bimodal pattern of perfusion distribution (closed circles) with areas with low $\dot{V}_A/\dot{Q}$ ratio due to the high cardiac output. $P\bar{v}O_2$ lay in the normal range and the hypoxaemia resulted from this low $\dot{V}_A/\dot{Q}$ mode.

Figure 2 Ventilation-perfusion distribution in another patient with pulmonary embolism. The percentage of vascular obstruction was 65% and the inert dead space was 47%. The blood flow (closed circles) and ventilation (open circles) are distributed in areas with high $\dot{V}_A/\dot{Q}$ ratios due to a low cardiac output and increased minute ventilation. Mixed venous $P\bar{v}O_2$ is low. The hypoxaemia stemmed from the low $P\bar{v}O_2$ and the $\dot{V}_A/\dot{Q}$ inequalities.

largely on the cardiac output (CO). There was a significant inverse relationship between the blood flow perfusing ventilated areas (cardiac output minus blood flow perfusing true shunt) and the mean value of the ventilation-perfusion ratio (mean $\dot{V}_A/\dot{Q}$ ratio). This finding indicates that CO greatly outweighs other contributory factors (increased ventilation, redistribution of alveolar ventilation from embolised to non-embolised regions, pulmonary vasoreactivity) that might affect $\dot{V}_A/\dot{Q}$ ratios and their distribution. Thus the $\dot{V}_A/\dot{Q}$ pattern in PE seems to be mainly influenced by passive consequences of the vascular obstruction: (1) redistribution of blood flow, when CO is increased or preserved, results in overperfusion of non-embolised regions with a concomitant appearance of low $\dot{V}_A/\dot{Q}$ units (fig 1); (2) for a fixed obstruction blood flow through low $\dot{V}_A/\dot{Q}$ compartment falls or even stops in response to a drop in CO. Under these conditions, $\dot{V}_A/\dot{Q}$ ratios tend to be higher than those observed in normal subjects at rest⁶ (fig 2). However, the greater the vascular obstruction, the larger must be the fall in CO to avoid overperfusion and hence low $\dot{V}_A/\dot{Q}$ mode in non-obstructed areas.

(2) *Dead space.* Vascular obstruction creates zones where alveoli are ventilated but not perfused. Alveolar ventilation is wasted and these unperfused areas must therefore be added to the anatomical dead space. However, in PE the percentage of the total ventilation that effectively exchanges gas in the perfused areas falls with increased pulmonary vascular obstruction. The $\dot{V}_A/\dot{Q}$ ratio of these areas is theoretically infinite, but in practice in the MIGET it is defined as a $\dot{V}_A/\dot{Q}$ ratio of over 100. In some areas there may be incomplete

vascular obstruction, which reduces perfusion, thereby increasing the $\dot{V}_A/\dot{Q}$ ratio. A significant proportion of the ventilation has now been measured in high $\dot{V}_A/\dot{Q}$ areas ($\dot{V}_A/\dot{Q} > 10$) in various inert gas studies.¹⁻⁴ These studies showed that there was a good correlation between the mean pulmonary vascular obstruction quantified on angiography by the Miller index⁷ and total dead space ventilation. However, the mean inert dead space was always found to be less than the percentage of obstruction observed on the angiograms. These findings suggest that alveolar ventilation is redistributed from occluded to non-obstructed areas. This shift in ventilation from the embolised areas is probably triggered by hypocapnia in the alveolar gas in the non-perfused or underperfused areas.

(3) *Intrapulmonary shunt.* Shunt is also frequently observed in the same acute phase, although it may be produced by different mechanisms such as oedema, alveolar collapse,²³ or opening of the foramen ovale.⁸ D'Alonzo *et al*² were the first to study the functional effects of acute, massive pulmonary embolism using the MIGET. In one of the two patients investigated within 24 hours of the acute episode, 20% of the cardiac output was shunt, although the chest radiograph was normal. In our series, the mean fraction of shunt was low (5.5(5.4)%), although individual values of 10%, 15%, and 13% were recorded. Animal studies have clearly shown the existence of pulmonary oedema during experimental pulmonary embolism, but there is no direct evidence for fully developed pulmonary oedema in man. In our case reported a few years ago,⁹ pulmonary oedema was noted in the permeable zones on the chest radiographs, suggesting that it was due to ex-

cessive perfusion (overperfusion) and/or pressure in the remaining non-obstructed areas. An alternative mechanism of intrapulmonary shunting is atelectasis, due to a combination of bronchoconstriction or atelectasis in the obstructed areas. Although we did not detect any regional infiltrates on chest radiographs in our series, we suspected that treatment may have led to some degree of reperfusion in the embolised and atelectatic regions.

Late phase:

Huet *et al*⁴ observed a moderate to severe amount of shunt (range 3–17% of CO) with radiographic evidence of atelectasis or alveolar filling in patients whose inert gas measurements were carried out two to 10 days after PE. However, these parenchymal alterations may have developed some time after the initial obstruction, and they may also have been a consequence of fibrinolytic therapy. Interestingly, we observed post-fibrinolytic reperfusion oedema in one patient with massive pulmonary embolism (fig 3). In the reperfused areas there was radiographic evidence of alveolar filling with oedema. The inert gas technique indicated that 24% of the blood flow was perfusing shunt. The gas exchange and radiographic abnormalities returned to normal within a few weeks. This observation suggests that reperfusion may lead to alveolar flooding, probably due to alterations in alveolar membrane permeability from the prolonged interruption of blood flow.

Determinants of hypoxaemia in the course of pulmonary embolism

In human studies the effects of acute embolism on overall gas exchange are not readily distinguishable from the effects of previous clots. Dantzker *et al*¹⁰ studied abnormalities in gas exchange over the two hours following experimental embolisation in 18 anaesthetised, mechanically ventilated dogs. There was no change in CO, mixed venous PO_2 remained constant, and the hypoxaemia was explained in terms of a change in $\dot{V}A/\dot{Q}$ distributions. Low $\dot{V}A/\dot{Q}$ ratios were observed but shunt was absent. Hypoxaemia may be increased by either high CO (decreasing the overall $\dot{V}A/\dot{Q}$ ratio) or low CO (decreasing the mixed venous oxygen

partial pressure). This balancing effect of CO on both intrapulmonary and extrapulmonary gas exchange leads to hypoxaemia. This decrease in Pao_2 may be enhanced in certain patients by some degree of shunt, possibly derived from the effects of a previous embolism. In any event, diffusion limitation to oxygen appears to play a minor part.³ Consideration of the results of these experimental and clinical studies suggests the following explanation for the gas exchange abnormalities arising during PE; except in rare cases of acute oedema or reopening of the foramen ovale, true shunt does not appear to occur in the acute phase of PE. At this stage of the disease hypoxaemia depends mainly on the extent of the low $\dot{V}A/\dot{Q}$ ratios and the drop in mixed venous PO_2 . In the subacute stage the ensuing shunt may become a supplementary cause of hypoxaemia even though the initial determinants are starting to regress as a result of reperfusion and cardiac output has returned to normal. In the absence of perfusion, alveolar dead space cannot participate in pulmonary gas exchange. If an embolus is, or becomes, partially occlusive, such an area is converted into a zone with high $\dot{V}A/\dot{Q}$ ratios. As the percentage of blood flow to these areas is low, their influence on arterial oxygen levels is minimal.

Effect of oxygen therapy

We have recently demonstrated that breathing 40% oxygen during the acute phase of PE leads to further alterations in pulmonary gas exchange.⁵ The main effect was a significant decrease in cardiac output with a concomitant slight improvement in $\dot{V}A/\dot{Q}$ relationships. Pulmonary vascular resistance did not change. We did not observe the expected effects of oxygen inhalation in these hypoxaemic patients. Although the effect of breathing 100% oxygen was not tested, the release of hypoxic pulmonary vasoconstriction by oxygen therapy might have been altered or masked by a pulmonary vasoconstrictor effect from a distension reflex and/or release of humoral mediators.

Effect of unilateral pulmonary artery occlusion

The diversity of the gas exchange abnormalities observed after pulmonary embolism prompted

Figure 3 Pulmonary angiograms (A) before and (B) after fibrinolytic treatment in a patient with pulmonary embolism. (A) Pulmonary angiogram, anterior view, demonstrating massive pulmonary embolism. (B) Pulmonary angiogram after treatment with thrombolytic agents. The right middle lobe artery was reperfused resulting in a regional pulmonary oedema in the same area.

us to examine the effect of experimental unilateral occlusion of the pulmonary artery.¹¹ In 10 patients studied prior to operation for bronchial carcinoma, cardiac output remained constant following inflation of balloon occlusion of one of the main pulmonary arteries. Moreover, although there was a significant increase in ventilated but non-perfused areas, the alveolar dead space evaluated by the MIGET was always significantly lower than the expected value based on the assumption of a more than 40% vascular obstruction. Furthermore, the expected overperfusion in the contralateral lung did not lead to any $\dot{V}_A/\dot{Q}$ abnormalities. Mean $\dot{V}_A/\dot{Q}$ and blood flow distribution remained constant. We therefore concluded that ventilation is better and more efficiently redistributed after balloon occlusion than after embolism, although the mechanism still remains uncertain.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Although most pulmonary emboli resolve, they continue to obstruct vessels to varying extents in a minority of patients. The thrombosed areas tend to become organised and endothelialised. Obstruction may develop after a single embolus or after recurrent emboli fail to resolve, and the end result in both situations is pulmonary hypertension. The original embolic event may not have been recognised, and patients may be erroneously diagnosed as having chronic lung disease or primary pulmonary hypertension.

The gas exchange impairment is characterised by a moderate $\dot{V}_A/\dot{Q}$ inequality with a hypoxaemic effect that is exacerbated by a low mixed venous $P\text{O}_2$ ($P\bar{V}\text{O}_2$).¹² Usually there is no intrapulmonary shunting, and an absence of zones of very low or very high $\dot{V}_A/\dot{Q}$ ratios. The dead space is increased. The lowered $P\bar{V}\text{O}_2$ from the cardiac impairment is a quantitatively significant determinant of the decreased Pao_2 that is commonly observed in such patients. Moreover, the marked fall in Pao_2 during exercise in these patients is also largely due to the influence of the fall in $P\bar{V}\text{O}_2$ on the abnormal lung units.¹³

EFFECT OF EXCESSIVE POLYCYTHAEMIA AND HAEMODILUTION

Although haemodilution induces an increase in cardiac output, its effects on gas exchange are largely unknown. In a study performed in Andean natives with polycythaemia and gross hypoxaemia¹³ we observed increases in both cardiac output and ventilation after haemodilution. The abnormal basal $\dot{V}_A/\dot{Q}$ distribution pattern (mainly due to hypoventilation) was improved a little, but Pao_2 remained unchanged despite a significant increase in total ventilation. These paradoxical results were assumed to be due to the combined effect of an insufficient reduction in haemoglobin concentration and a high residual $\dot{V}_A/\dot{Q}$ mismatch. To our knowledge there are no reports in the literature on the effect of haemodilution in polycythaemic COPD patients at sea level. A study of this

kind would not be easy to carry out on a large series of patients and, in any case, polycythaemia in hypoxaemic patients with COPD is now effectively prevented by oxygen therapy. Nevertheless, our data and simulations suggested that the reduction in haemoglobin concentration by haemodilution in polycythaemic patients at sea level ($\text{Pto}_2 = 150$ mm Hg) led to a greater improvement in Pao_2 for the same degree of $\dot{V}_A/\dot{Q}$ inequalities than that observed in our polycythaemic Andean natives.

Diseases with structural abnormalities in pulmonary vessels

PRIMARY PULMONARY HYPERTENSION (PPH)

In idiopathic pulmonary hypertension Pao_2 may fall in the later stages of the disease, although $\dot{V}_A/\dot{Q}$ inequalities tend to be moderate.¹⁴ MIGET studies have now shed more light on the mechanisms underlying the disturbances in gas exchange stemming from these abnormalities of the vascular bed. In patients suffering from chronic obliterative pulmonary vascular disease Dantzker *et al* showed that much of the cardiac output was distributed to lung units with near normal $\dot{V}_A/\dot{Q}$ ratios, while only a small percentage (mean <10%) circulated through underventilated or unventilated areas (shunt).¹⁴ Administration of oxygen, isoproterenol, nitroprusside,¹⁵ or nifedipine¹⁶ worsened $\dot{V}_A/\dot{Q}$ relationships due to a reduction in pulmonary vascular tone and an increased blood flow in very low $\dot{V}_A/\dot{Q}$ units and/or shunt. This deleterious effect of pulmonary vasodilatation was not accompanied by a negative effect on arterial oxygenation as the vasodilators also increased cardiac output. The resultant increase in mixed venous oxygen content raised the end capillary arterial Po_2 in low $\dot{V}_A/\dot{Q}$ units, thus preventing the decrease in arterial Po_2 that would otherwise have occurred. These two studies indicated that most subjects with chronic obstruction of the pulmonary vascular beds have increased pulmonary vascular tone, which in turn contributes to the maintenance of ventilation-perfusion matching in the lungs. Any reduction in arterial Po_2 was thus assumed to be mainly due to the low mixed venous Po_2 caused by the greatly reduced cardiac output. An inert gas study¹⁴ performed during exercise in patients with chronic pulmonary hypertension corroborated the key role of the decreased $P\bar{V}\text{O}_2$ due to an inadequate cardiac output when workload increases without significant change in $\dot{V}_A/\dot{Q}$ inequalities.

LIVER CIRRHOSIS

Although it is thought that there is some connection between primary pulmonary hypertension and portal hypertension secondary to hepatic cirrhosis,¹⁷ the gas exchange abnormalities observed in patients with liver cirrhosis appear to be related more to a decrease in pulmonary vascular tone.

Patients with liver cirrhosis are sometimes severely hypoxaemic. Decrease in oxy-

Figure 4 $\dot{V}_A/\dot{Q}$ distribution pattern in a patient with left ventricular failure before the onset of pulmonary oedema. High $\dot{V}_A/\dot{Q}$ ratios cancel the effect of a low $\bar{P}\dot{v}O_2$ and prevent the decrease in PaO_2 (see text).

haemoglobin affinity, alveolar end capillary diffusion limitation, air trapping, and increased closing volume¹⁸ are generally insufficient to account for the degree of desaturation in hypoxaemic patients. Other potential causes are arteriovenous anastomoses,¹⁹ failure of hypoxic pulmonary vasoconstriction,²⁰ or both. A MIGET study of 15 patients with normal PaO_2 ²¹ indicated that the $\dot{V}_A/\dot{Q}$ abnormalities stemmed largely from the abnormal behaviour of the pulmonary circulation. An increase in blood flow in lung units with low $\dot{V}_A/\dot{Q}$ was observed in the patients with the most severe hepatic impairment. The greater the liver dysfunction the lower the pulmonary vascular response to hypoxia. Thus, there is a greater $\dot{V}_A/\dot{Q}$ mismatch in the patients with severely altered hepatic function, and they are correspondingly more hypoxaemic. Mélot *et al*²² made similar observations in moderately hypoxaemic cirrhotic patients. These conclusions are also supported by the results of two similar studies^{23,24} on severely hypoxaemic patients. In our study the cirrhotic patients with normal conventional pulmonary function tests had very low PaO_2 (<60 mm Hg). These patients had a high cardiac output, minimal pulmonary vascular tone, and a mild to moderate $\dot{V}_A/\dot{Q}$ inequality in perfused and ventilated areas. The hypoxaemia of these patients was essentially due to a marked shunt (mean shunt, 20% of CO) or, in two cases, to poorly ventilated areas. These results suggested that the cirrhotic patients have an impairment in the regulation of pulmonary vascular tone, possibly via a humoral mechanism. Edell *et al*²⁴ found the same pattern of gas exchange abnormalities accompanied by an abnormal vascular reactivity with loss of hypoxaemic pulmonary vasoconstriction in some patients. A small degree of oxygen diffusion limitation was observed in both studies, which accounted for some of the hypoxaemia.

A recent animal study²⁵ has shown that substances metabolised by the liver are involved in the regulation of pulmonary vascular tone and reactivity. Normalisation of liver function should therefore tend to correct systemic and pulmonary vascular abnormalities and alterations in $\dot{V}_A/\dot{Q}$ distributions. Eriksson *et al*²⁶ evaluated intrapulmonary shunt and $\dot{V}_A/\dot{Q}$ relationships before and after liver transplantation in six patients. After transplantation the hyperkinetic circulatory syndrome disappeared, accompanied by a decrease in cardiac output and an increase in systemic and pulmonary vascular resistance. PaO_2 returned to normal in all patients, and both shunt and low $\dot{V}_A/\dot{Q}$ relationships were reduced (the sum of shunt and low $\dot{V}_A/\dot{Q}$ units fell from a mean of 11.8% preoperatively to 0.6% of CO postoperatively). These results added further support to the other studies that suggest a direct functional relationship between the respiratory and cardiovascular alterations in patients with liver disease.

Pulmonary gas exchange in cardiac disease

The salient physiological abnormality in pulmonary vascular disease from an acquired heart condition is pulmonary venous hypertension. Mitral stenosis and left ventricular failure of any aetiology are the main culprits. There are only a few reports of inert gas studies of the gas exchange abnormalities in such patients. Nevertheless, it would be logical to assume that any disturbances stem from the fall in cardiac output. In dogs with a baseline $\dot{V}_A/\dot{Q}$ distribution within normal limits, alterations in cardiac output were induced first by bleeding followed by reinfusion of blood.²⁷ PO_2 was remarkably well maintained during haemorrhage, despite a 75% fall in cardiac output. The authors offered no convincing explanation for this phenomenon. After reinfusion cardiac output rose to above control values, but there was no evidence of appreciable shunt or perfusion to low $\dot{V}_A/\dot{Q}$ areas. PaO_2 remained in the normal range. Under these circumstances, the large change in oxygen transport did not lead to a large fall in PaO_2 as the interaction between $\bar{P}\dot{v}O_2$ and $\dot{V}_A/\dot{Q}$ distribution effectively regulates the overall PaO_2 in the normal lung. In humans most of the reports deal with $\dot{V}_A/\dot{Q}$ relationships after cardiac surgery.²⁸⁻³¹ The results are quite comparable to those observed in dogs, although the baseline distributions displayed some degree of $\dot{V}_A/\dot{Q}$ inequalities. We have reported a case of left ventricular failure in a patient with no clinical or radiological evidence of pulmonary oedema (personal communication). Right heart catheterisation detected post-capillary pulmonary hypertension with a decreased cardiac index: mean pulmonary artery, pulmonary capillary wedge and right atrial pressures were 36, 25, and 5 mm Hg, respectively. Pulmonary vascular resistance lay within the normal range. Inert gas measurements demonstrated a high $\dot{V}_A/\dot{Q}$ ratio distribution. The mean $\dot{V}_A/\dot{Q}$ values for both blood flow and ventilation were 2 and 2.7 respectively. This

pattern of distribution (fig 4) maintained a normal P_{aO_2} (78 mm Hg) in the presence of a lowered P_{vO_2} due to the inadequate cardiac output and the impaired peripheral gas exchange. It is now established³² that the effect of a reduced P_{vO_2} on P_{aO_2} can be offset by the great increase in $\dot{V}_A/\dot{Q}$ ratio resulting from the combined effect of increased ventilation and decreased cardiac output as it is currently observed in cardiogenic shock.

Conclusion

The results from MIGET studies on patients with different pulmonary vascular pathologies point to the key role of cardiac output on overall respiratory gas exchange. The cardiac output will be conditioned by both structural alterations in the pulmonary vascular bed and the changes in resistance induced by the disease. In vascular lung diseases the pattern of $\dot{V}_A/\dot{Q}$ ratio distributions and a low mixed venous P_{O_2} are the two main factors underlying the impairment in gas exchange. In primary cardiac diseases the normal lung maintains P_{aO_2} by efficient adjustment of the $\dot{V}_A/\dot{Q}$ distribution to the fall in cardiac output.

The authors thank Mrs Patricia Bordes for her secretarial assistance.

- McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. *Am J Cardiol* 1971;28:288-94.
- D'Alonzo GE, Bower JS, Dehart P, Dantzker DR. The mechanism of abnormal gas exchange in acute massive pulmonary embolism. *Am Rev Respir Dis* 1983;128:170-2.
- Manier G, Castaing Y, Guénard H. Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. *Am Rev Respir Dis* 1985;132:332-8.
- Huet Y, Lemaire F, Brun Buisson C, Knaus WA, Teisseire B, Payen D, Mathieu D. Hypoxemia in acute pulmonary embolism. *Chest* 1985;88:829-36.
- Manier G, Castaing Y. Influence of cardiac output on oxygen exchange in pulmonary embolism. *Am Rev Respir Dis* 1992;145:130-6.
- Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation perfusion ratios in normal subjects breathing air and 100% O_2 . *J Clin Invest* 1974;54:54-68.
- Tibbitt DA, Fletcher EWL, Thomas ML, Sutton GC, Miller GAH. Evaluation of a method for quantifying the angiographic severity of major pulmonary embolism. *Am J Radiol* 1975;125:895-9.
- Herve PH, Petipretz P, Simonneau G, Salmeron S, Laine JF, Duroux P. The mechanisms of abnormal gas exchange in acute massive pulmonary embolism. *Am Rev Respir Dis* 1983;128:1101.
- Manier G, Mora B, Castaing Y, Guénard H. Oedème pulmonaire au cours d'une embolie pulmonaire. *Bull Eur Physiopathol Respir* 1984;20:55-60.
- Dantzker DR, Wagner PD, Tornabene VW, Alazraki NP, West JB. Gas exchange after pulmonary thromboembolization in dogs. *Circ Res* 1978;42:92-103.
- Cochard JF, Chidier H, Manier G. Adaptation ventilatoire secondaire à l'occlusion unilatérale de l'artère pulmonaire. *J Physiol (Paris)* 1987;82:19A.
- Kapitan KS, Buchbinder M, Wagner PD, Moser KM. Mechanisms of hypoxemia in chronic thromboembolic hypertension. *Am Rev Respir Dis* 1989;139:1149-54.
- Dantzker DR, d'Alonzo GE, Bower JS, Popat K, Crevey BJ. Pulmonary gas exchange during exercise in patients with chronic obstructive pulmonary hypertension. *Am Rev Respir Dis* 1984;130:412-6.
- Manier G, Guénard H, Castaing Y, Varène N, Vargas E. Pulmonary gas exchange in Andean natives with excessive polycythemia, effect of haemodilution. *J Appl Physiol* 1988;65:2107-17.
- Dantzker DR, Bower JS. Pulmonary vascular tone improves $\dot{V}_A/\dot{Q}$ matching in obstructive pulmonary hypertension. *J Appl Physiol* 1981;51B:607-13.
- Mélot C, Naeije R, Mols P, Vanderbossche JL, Denolin H. Effects of nifedipine on ventilation/perfusion matching in primary pulmonary hypertension. *Chest* 1983;83:203-7.
- MacDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? *Am Rev Respir Dis* 1983;127:437-41.
- Heinemann HD, Emerigic C, Mijnsen JP. Hyperventilation and arterial hypoxemia in cirrhosis of the liver. *Am J Med* 1960;28:239-46.
- Rydell R, Hoffbauer FW. Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *Am J Med* 1956;21:450-60.
- Daoud FS, Reeves JT, Schefer JW. Failure of hypoxic pulmonary vasoconstriction in patients with liver cirrhosis. *J Clin Invest* 1972;51:1076-80.
- Rodriguez-Roisin R, Roca J, Agustí AGN, Mastai R, Wagner P, Bosch J. Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. *Am Rev Respir Dis* 1987;135:1085-92.
- Mélot C, Naeije R, Dechamps P, Hallemans R, Lejeune P. Pulmonary and extrapulmonary contributors to hypoxemia in liver cirrhosis. *Am Rev Respir Dis* 1989;139:632-40.
- Castaing Y, Manier G. Hemodynamic disturbances and $\dot{V}_A/\dot{Q}$ matching in hypoxemic cirrhotic patients. *Chest* 1989;96:1064-9.
- Edell ES, Cortese DA, Krowka MJ, Rehder K. Severe hypoxemia and liver disease. *Am Rev Respir Dis* 1989;140:1631-5.
- Chang SW, Ohara N. Pulmonary circulatory dysfunction in rats with biliary cirrhosis. An animal model of the hepatopulmonary syndrome. *Am Rev Respir Dis* 1992;145:798-805.
- Eriksson LS, Soderman C, Ericzon BG, Eleborg L, Wahren J, Hedenstierna G. Normalization of ventilation/perfusion relationships after liver transplantation in patients with decompensated cirrhosis: evidence for a hepatopulmonary syndrome. *Hepatology* 1990;12:1350-7.
- Fortune JB, Mazzone RW, Wagner PD. Ventilation-perfusion relationships during hemorrhagic hypotension and reinfusion in the dog. *J Appl Physiol: Respir Environ Exerc Physiol* 1983;54:1071-82.
- McEvoy RD, Drew MJR, Mahar LJ. The effects of exercise on ventilation-perfusion relationship in patients with mitral stenosis. *Bull Eur Physiopathol Respir* 1986;22:239-46.
- Anjou-Lindskog E, Broman L, Holmgren A, Wedelin B. Effects of Prenatal on central haemodynamics and $\dot{V}_A/\dot{Q}$ distribution early after open-heart surgery. *Acta Anaesthesiol Scand* 1983;27:142-8.
- Anjou-Lindskog E, Broman M, Holmgren A. Effects of oxygen on central haemodynamics and $\dot{V}_A/\dot{Q}$ distribution after coronary bypass surgery. *Acta Anaesthesiol Scand* 1983;27:378-84.
- Gillespie DJ, Didier EP, Rehder K. Ventilation-perfusion distribution after aortic valve replacement. *Crit Care Med* 1990;18:136-40.
- West JB. Ventilation-perfusion relationships. *Am Rev Respir Dis* 1977;116:919-43.